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A Pd-Catalyzed Synthesis of Functionalized Piperidines**

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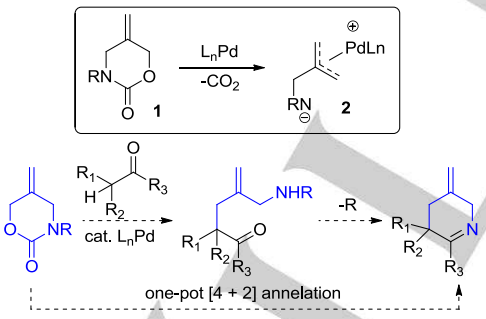
Abstract: A readily available cyclic carbamate **1** functions as a general precursor to a range of functionalized piperidine products via a new Pd-catalyzed annulation strategy. An asymmetric catalytic variant provides a rapid and efficient means to access these heterocycles with high to excellent levels of enantiocontrol. Finally, these richly functionalized compounds are amenable to further chemoselective elaboration.

Recent trends in drug discovery design have moved away from targets that are rich in aromatic sub-units, and more towards intermediates that are rich in sp^3-containing scaffolds.[1] This change in target properties has led to a demand for rapid and efficient techniques for the synthesis of lead-like structures that contain functional groups that allow lead optimization to be performed in a systematic and straightforward manner. In this context, we have reported the employment of a formal [3 + 3] cycloaddition of aziridines that allows chiral piperidines to be prepared with excellent enantiocontrol.[2,3] However, this method requires enantioenriched aziridine substrates to be made available. In an effort to devise an enantioselective variant, we considered a formal [4 + 2] strategy that comprised a Pd-catalyzed allylation – condensation sequence (Scheme 1). Moreover, we envisaged that the required conjunctive reagent **2** could be accessed from carbamate **1**, allowing its generation in situ and offering the potential for enantiocontrol through the employment of chiral ligands. This approach would complement existing Pd-catalysed routes to chiral heterocycles that exploit catalyst generated dipolar reagents.[4] For example, Aggarwal has recently reported a stereoselective route to chiral functionalized *pyrrolidines* using a formal [3 + 2] reaction of alkenyl aziridines and Michael acceptors.[5]



Scheme 1. Pd-catalyzed annulation strategy to chiral piperidines.

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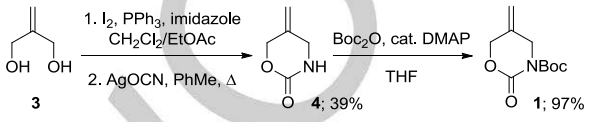
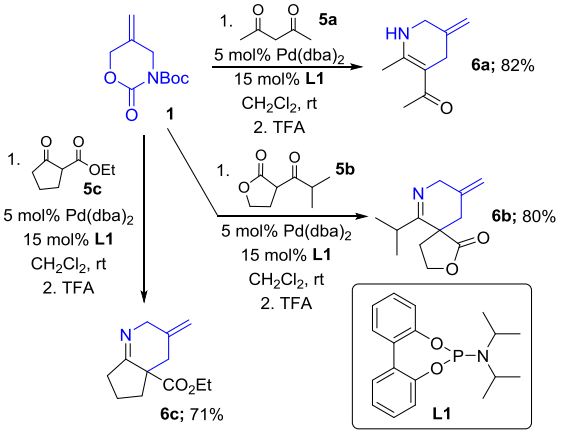
Our first task was to devise an efficient route to compound **1**, a precursor to the required dipolar intermediate. In the event we were able to adapt the sequence developed by Suzuki[6] to establish a short and scalable route to carbamate **4** that provided the opportunity to access the *N*-activated reagent **1** (Scheme 2).



Scheme 2. Synthesis of annulation precursor **1**.

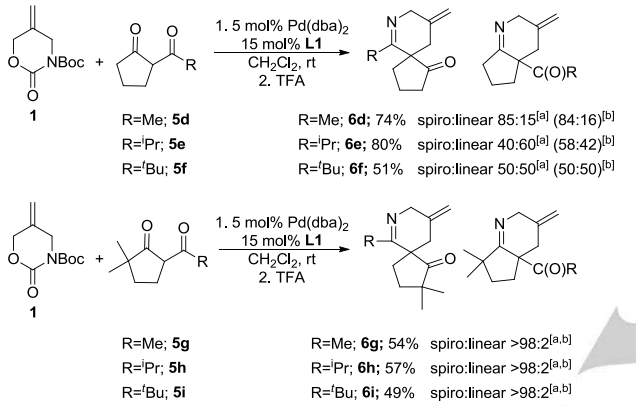
Turning our attention to the key annulation reaction, a small family of 1,3-dicarbonyl substrates comprising diketones and β-keto esters were employed in our preliminary scoping studies, our results are shown in Scheme 3. After preliminary catalyst optimization, we were delighted to find that carbamate **1** could be smoothly transformed into a range of products using a catalyst system comprising $Pd(dba)_2$ and readily available phosphoramidite ligand **L1**. Specifically, pentane-2,4-dione **5a** underwent a one-pot allylation-condensation sequence to deliver piperidine **6a** in high yield. When the same procedure was employed on lactone **5b** a spirocyclic heterocycle **6b** was generated, whilst an ester substituted cyclic ketone **5c** produced a linearly fused bicycle **6c**. Therefore, these preliminary studies confirmed the potential of cyclic carbamate **1** to deliver a range of piperidine products whereby the product skeleton could be dictated by the type of 1,3-dicarbonyl compound used.



Scheme 3. Preliminary studies on the scope of the Pd-catalyzed annulation reaction.

The condensation steps in reactions of **5b,c** shown in Scheme 3 are chemoselective for reaction at the ketone over the ester group. We therefore wanted to establish that selective imine

formation could also be achieved when unsymmetrical 1,3-diketones were used. Accordingly, we opted to investigate the annulation reaction of a series of α-acylated cyclopentanones and our results are shown in Scheme 4. The annulation of substrates **5d-f** provided a mixture of products in each case. Fortunately, the products could be separated in the case of **6e,f** via flash column chromatography allowing their characterization as individual compounds.[7] The spiro:linear product ratios reflect the thermodynamic stabilities of the individual compounds, and we noted that neat samples of pure spiro and linear compounds isomerized back to the original ratios within a few days at room temperature. Interestingly however, the outcome of these condensation reactions is subject to steric control. Specifically, we subjected a family of 5-acyl-2,2-dimethylcyclopentanones **5g-i** to the allylation-condensation procedure and were pleased to find that the spiropiperidine products were formed exclusively in each case (Scheme 4).

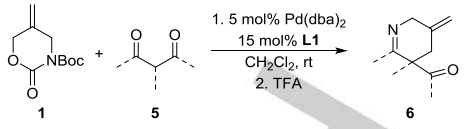


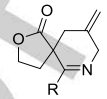
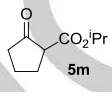
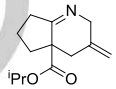
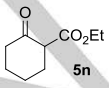
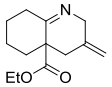
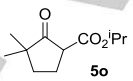
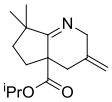
Scheme 4. 1,3-Diketone annulation reactions. [a] Ratio of crude mixtures as judged by 400 MHz ^{1}H NMR spectroscopy; [b] Ratios of isolated products.

As β-keto ester substrates provided predictable reactivity patterns we decided to explore the scope of the one-pot allylation-condensation procedure on these compounds and our results are shown in Table 1. α-Acyl-γ-butyrolactones **5j-l** provided the corresponding spirocyclic piperidines **6j-l** in good yield (entries 1-3). These compounds are of potential biological interest as they have recently been shown to exhibit acetyl-CoA carboxylase inhibitory activity.[8] Ketoester substrates **5m-o** were also successfully employed, giving rise to linearly fused bicyclic products **6m-o**. Finally, we were pleased to find that α-aryl cyclic ketones could also function as substrates in this annulation process. Preliminary studies in this class of compound showed that bicyclic heterocycle **6p** could be formed in acceptable yield after annulation of **5p** and reduction of the resulting imine group with $NaBH_4$ (entry 7).

As we envisaged that the annulation process proceeded via an intermediate Pd-π-allyl intermediate, we were interested in the prospect of developing an enantioselective variant of this piperidine forming reaction. Previous studies in this area using unsymmetrical Pd-π-allyl complexes have demonstrated the difficulty in inducing high degrees of enantioselectivity with 1,3-dicarbonyl substrates, in part due to the distal approach of the prochiral nucleophile to the palladium,[9] which contains all of the chiral information, but also due to the relative steric and electronic symmetry which is inherent in these substrates.[10]

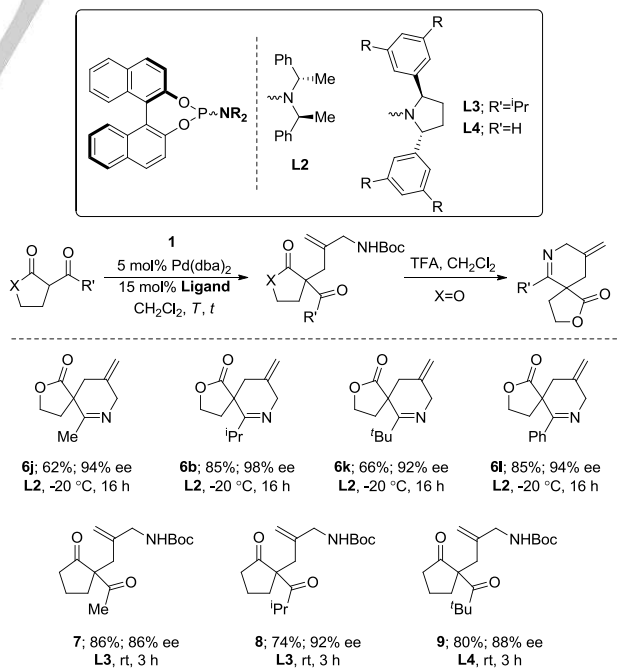
Table 1. Pd-catalyzed synthesis of quaternary carbon-substituted allylic amine derivatives.



entry	substrate	product	yield[a]
1		R=Me; **5j** 	**6j;** 86%
2		R=^{t}Bu; **5k**	**6k;** 56%
3		R=Ph; **5l**	**6l;** 94%
4	 **5m**		**6m;** 75%
5	 **5n**		**6n;** 70%
6	 **5o**		**6o;** 57%
7	 **5p**		**6p;** 44%[b]

[a] Yields of isolated products; [b] Crude reaction product treated with $NaBH_4$. [c] Step 1 was performed at reflux.

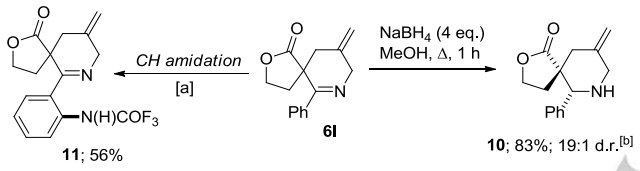
Nonetheless, an initial ligand screen indicated that **L2** could perform this transformation with impressive degrees of enantiodiscrimination at -20 °C. We were interested to find that



Scheme 5. Enantioselective piperidine synthesis.

increasing the steric encumbrance on the ketone had varying effects on the selectivity with the isopropyl group giving rise to the best enantiomeric excess we achieved. Additionally, ligands derived from chiral diarylpyrrolidines (**L3** and **L4**) were found to be effective for the enantioselective allylation of the 1,3-diketone substrates. The sterically demanding substrate **5f** was unreactive with **L3** in this case, and so the ligand **L4** was employed to provide the product with high enantioselectivity. Efforts to exploit enantioenriched compounds **7-9** in selective annulation reactions (cf Scheme 4) have not been successful to-date but are the subject of active investigation.

Compound **6l** was used to investigate functionalization of these compounds in order to further demonstrate the utility of this chemistry. We found that treatment of **6l** with $NaBH_4$ in refluxing methanol afforded the two diastereomeric piperidine products in a 19:1 ratio. Chromatographic separation afforded only the major diastereomer **10** in an excellent yield.[11] Additionally, the imine is unusually stable and can be utilized as a directing group for C-H amidation. Indeed, using Rh-catalysis[12] we installed a trifluoroacetamide group in the *ortho*-position on the aromatic moiety.



Scheme 6. Imine functionalization; [a] $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $PhI(OAc)_2$ (1.5 eq.), CF_3CONH_2 (1.0 eq.), CH_2Cl_2, 40 °C, o/n; [b] diastereomer ratio determined 400 MHz ^1H NMR spectroscopy.

In conclusion, we have demonstrated the ability of carbamate **1** to deliver a range of highly functionalised piperidine products via a simple Pd-catalyzed annulation strategy. This methodology is very versatile and allows access to a range of sp^3-containing scaffolds that bear useful functionality for further derivatization. In this context, we have demonstrated that the imine group can be exploited in a diastereoselective reduction as well as in a rare example of an imine-directed C-H amidation reaction. Additionally, we have shown that chiral phosphoramidite ligands produce spiropiperidines with excellent enantioselectivities, thereby offering an expedient means to access this important class of compounds with control of the quaternary stereocenter.

Experimental Section

Typical allylation-condensation procedure as exemplified by the formation of 6j: To a flask charged with $Pd(dba)_2$ (7 mg, 0.012 mmol) and **L1** (11 mg, 0.035 mmol) was added CH_2Cl_2 (3 mL) and the mixture was allowed to stir for 5 min. Carbamate **1** (50 mg, 0.234 mmol) in CH_2Cl_2 (1 mL) was added, followed by α-acetyl-γ-butyrolactone (60 mg, 0.469 mmol) and the reaction mixture was left to stir for 3 h at rt. TFA (1 mL) was added and the reaction mixture was left to stir for an additional 1 h. The reaction was quenched by the addition of sat. $NaHCO_3$ (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (75% ethyl acetate in petrol) to afford 6-methyl-9-methylene-2-oxa-7-azaspiro[4.5]dec-6-en-1-one **6j** (26 mg, 62%) as a colourless oil. FTIR ν_{max} (thin film/cm^{-1}) 2966, 1732, 1655, 1455; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 1H, C=C$\underline{H_A}H_B$), 4.84 (s, 1H, C=C$H_A\underline{H_B}$), 4.25 (d, J = 19.5 Hz, 1H, NC$\underline{H_A}H_B$), 4.15 (d, J = 19.5 Hz, 1H, NC$H_A\underline{H_B}$), 2.51 – 2.27 (m, 3H, C=CC$\underline{H_A}H_B$, C$\underline{H_2}$), 2.21 – 1.90 (m, 5H, C=CC$H_A\underline{H_B}$, 2 × C$\underline{H_2}$), 1.90 – 1.80 (m, 3H, C$\underline{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.7, 166.2, 139.4, 110.8, 58.5, 55.5, 39.0, 36.7, 33.7, 23.4, 19.3; MS (ESI^+) 178 ($M+H^+$, 100%); HRMS (ESI^+) $C_{11}H_{15}NO$ requires $M+H^+$ 178.1232, found 178.1235.

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[11] The structure of **10** was confirmed by X-ray crystallographic analysis. CCDC-1475348 contains the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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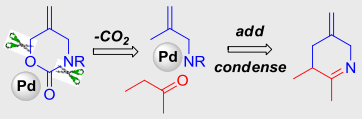
COMMUNICATION



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